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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/070,629	04/30/1998	PETER PALESE	6923-071-999	4644

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EXAMINER	
SCHEINER, LAURIE A	

ART UNIT	PAPER NUMBER
1648	34

DATE MAILED: 11/18/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No. 09/070,629	Applicant(s) Palese et al.
	Examiner Laurie Scheiner	Art Unit 1648

-- Th MAILING DATE f this communication appears on the cover sheet with the c rrespondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136 (a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1) ☒ Responsive to communication(s) filed on *Jul 14, 2003* .

2a) ☒ This action is **FINAL.** 2b) ☐ This action is non-final.

3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under ***Ex parte Quayle***, 1935 C.D. 11; 453 O.G. 213.

Disposition of Claims

4) ☒ Claim(s) *1 and 30-54* is/are pending in the application.

4a) Of the above, claim(s) *30-54* is/are withdrawn from consideration.

5) ☐ Claim(s) _____ is/are allowed.

6) ☒ Claim(s) *1* is/are rejected.

7) ☐ Claim(s) _____ is/are objected to.

8) ☐ Claims _____ are subject to restriction and/or election requirement.

Application Papers

9) ☐ The specification is objected to by the Examiner.

10) ☐ The drawing(s) filed on _____ is/are a) ☐ accepted or b) ☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11) ☐ The proposed drawing correction filed on _____ is: a) ☐ approved b) ☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12) ☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13) ☐ Acknowledgement is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a) ☐ All b) ☐ Some* c) ☐ None of:

1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____ .
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

*See the attached detailed Office action for a list of the certified copies not received.

14) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. § 119(e).

a) ☐ The translation of the foreign language provisional application has been received.

15) ☐ Acknowledgement is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s). _____
4) ☐ Interview Summary (PTO-413) Paper No(s). _____
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

Claim 1 is considered below.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claim 1 is rejected under 35 U.S.C. 112, first paragraph, because the specification does not reasonably enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with the claim for reasons of record.

Applicant's arguments filed July 14, 2003 have been fully considered but they are not persuasive.

Also, the declaration of Dr. Adolfo Garcia-Sastre, filed under 37 CFR 1.132, is acknowledged. The declaration, however, is unpersuasive since the data contained therein is not commensurate in scope with that which is instantly claimed. That is, the construction of a recombinant influenza virus which expresses the HER-2 E75 epitope fails to correspond with the instantly recited influenza construct wherein any tumor-associated antigen is encoded.

Claim 1 is drawn toward a recombinant influenza virus containing a region which encodes any tumor-associated antigen. The claim is not drawn to a recombinant influenza virus containing a region which encodes the HER-2 E75 epitope as set forth in the declaration.

Rao et al. (J. Immunol. **156**:3357-3365, 1996) when discussing applicants' experimental model teach that "[i]t is important to realize that the tumor model system in which these studies were completed is artificial. β-*gal* represents a large xenogeneic Ag introduced into a tumor cell line and tested in syngeneic animals, whereas many of the human TAAs cloned thus far, as well

as the mouse Ag PIA, are nonmutated "self" proteins. Thus, the question arises as to whether data derived from the use of such a foreign Ag as a TAA will have relevance to the human situation in which most TAAs appear to be predominantly self Ags. It is worth noting, however, that similar systems, although using foreign proteins as model TAAs, have been instructive, e.g., transfection of the NP gene from vesicular stomatitis virus into EL4 thymoma or transfection of the human carcinoembryonic Ag (CEA) into MC38, a murine adenocarcinoma. Interestingly, the host response to challenge with either CT26.WT or CT25.CL25, expressing β-*gal*, was unaltered, and we found no evidence of systemic immunity elicited to β-*gal*. Both CT26.WT and CT26.CL25 grow equally well and are equally lethal after i.v. injection. Indeed, the β-*gal* model system may be most relevant to human tumors possessing TAAs that originate from viruses, fusion proteins resulting from translocations, or genetic events that result in the expression of foreign proteins arising from mutations, frame-shifts, translation of introns, and the loss of stop codons." It is noted, however, that applicants' disclosure fails to provide any support of influenza A recombinants containing TAAs that originate from viruses, etc.

Restifo (Current Opinion in Immunology, 1996, **8**:658-663) teaches at page 660 that there are concerns with respect to anti-cancer vaccines which are not yet adequately addressed in animal models. "The first concerns the duration of tumors in humans. Whereas tumor deposits may exist for years in humans before they are treated, or even detected, the time course studied in mice is generally measured in weeks and sometimes even in days. The longer kinetics of the tumor-bearing state could increase the heterogeneity of the tumor cells, resulting in cell to cell differences that include antigen expression and antigen processing and presenting efficiency. Human tumor cells can escape immune recognition by a number mechanisms, including loss of β2-microglobulin, down regulation or loss of the expression of particular HLA

class I loci, and down regulation, mutation or deletion of the proteasome component molecules latent membrane proteins -2 and -7 as well as of transporters associated with antigen processing. Prior chemotherapy or radiotherapy could complicate problems related to the mutability of tumor cells. Such mutability can result in powerfully resistant tumor cells when the number of tumor cells are counted in trillions. Furthermore, when tumor weight is measured in kilograms rather than in grams or milligrams, issues of peripheral tolerance as well as other forms of specific and nonspecific immunosuppression could be qualitatively different."

Moreover, the disclosure fails to meet the legal requirements dictating that the scope of the claims must bear a reasonable correlation to the scope of enablement provided by the specification. *In re Fisher,* 427 F.2d 833, 839, 166 U.S.P.Q. 18, 24 (C.C.P.A. 1970). *In re Vaeck,* 20 U.S.P.Q.2d 1438 (C.A.F.C. 1991). *In re Angstadt*, 537 F.2d 498, 502-03, 190 U.S.P.Q. 214, 218 (C.C.P.A. 1976). The court stated in *In re Vaeck* that "there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. This means that the disclosure must adequately guide the art worker to determine, without undue experimentation, which species among all those encompassed by the claimed genus possess the disclosed utility. Where, as here, a claimed genus represents a diverse and relatively poorly understood group of tumor associated antigens, the required level of disclosure will be greater than, for example, the disclosure of an invention involving a "predictable" factor such as a mechanical or electrical element." The disclosure fails to provide sufficient guidance pertaining to the molecular determinants modulating the cancer suppressive activity of any given recombinant influenza virus containing sequence encoding any given TAA, the disclosure fails to provide sufficient guidance pertaining to those variants or derivatives that can reasonably be

expected to have and retain suppressive activity. Furthermore, the prior art fails to provide sufficient guidance pertaining to the structural requirements of analogous elements. Thus, the skilled artisan could not possibly predict the nucleotide sequence of various functional equivalents. Accordingly, when all the aforementioned factors are considered together, it would clearly require undue experimentation to practice the claimed invention.

The examiner disagrees with applicants' positions since the breadth of the claimed invention is excessive and encompasses a large genus of compounds which do not receive adequate written support and are clearly not enabled. No description of the tumor-associated gene being operably linked to a promoter has been set forth and the claims can encompass heterologous polynucleotides of varying lengths, allelic variants of any of these sequences, and sequences that have been modified to contain nucleotide additions, subtractions, and/or replacements, none of which are adequately supported by the disclosure. The claims encompass an inordinate number of species which have not been adequately described. The claimed limitations are so vague and indefinite that they fail to bear a reasonable correlation to the scope of enablement provided by the specification. That is, there must be sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and how to use the invention as broadly as it is claimed. Moreover, applicants fail to provide a teaching for the structure of the polynucleotides expressing the intended antigens. The examiner contends that one of skill cannot reproduce that which has not been described. That is, it is evident that applicants were not in possession of that which is claimed at the time of the invention. It is well settled that the claimed subject matter need not be supported by an explicit, word for word recitation, but something more than a suggestion is needed to satisfy the

requirement for an adequate written description. As set forth in Lockwood v. American Airlines Inc., 107 F.3d 1565, 1571-1572, 41 USPQ2d 1961, 1966 (Fed. Cir. 1997):

> It is the disclosures of the applications that count. Entitlement to a filing date extends only to that which is disclosed. While the meaning of terms, phrases, or diagrams in a disclosure is to be explained or interpreted from the vantage point of one skilled in the art, all the limitations must appear in the specification. Rather, a[n]... application itself must describe an invention, and do so in sufficient detail that one skilled in the art can clearly conclude that the inventor invented the claimed invention as of the filing date sought... [A]ll that is necessary to satisfy the description requirement is to show that one is "in possession" of the invention... One shows that one is "in possession" of the invention by describing the invention, with all its claimed limitations, not that which makes it obvious. . . Although the exact terms need not be used in haec verba, . . . the specification must contain an equivalent description of the claimed subject matter. [Citations omitted]

It is not sufficient for purposes of the written description requirement of Section 112 that the disclosure, when combined with knowledge in the art, would lead one to speculate as to modifications that the inventor might have envisioned, but failed to disclose. Each application must describe the claimed features.

Regarding enablement, applicants essentially argue that their compounds and constructs are enabled since all components for making are known and have been set forth. The examiner contends that enablement is met by teaching how to make and use the claimed compounds rather than teaching the individual components employed in making the final product. Moreover, applicants have, in fact, not provided the necessary precursor components. That is, the claims are broad and the polynucleotide variants (including the influenza sequences, as well

as the sequences encoding the tumor antigens) that when combined to make the final product have not been taught. Applicants' assertion that any experimentation required to practice the invention is routine is clearly incorrect since undue experimentation would be required.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Laurie Scheiner, whose telephone number is (703) 308-1122. Due to a flexible work schedule, the examiner's hours typically vary each day. However, the examiner can normally be reached Monday thru Friday. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. Any inquiry of a general nature or relating to the status of this application should be directed to the Group 1600 receptionist whose telephone number is (703) 308-0196.

Correspondence related to this application may be submitted to Group 1600 by facsimile transmission. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). Official communications should be directed toward one of the following Group 1600 fax numbers: (703) 308-4242, (703) 305-3014, (703) 872-9306 or (703) 872-9307. Informal communications may be submitted directly to the Examiner through the following fax number: (703) 746-5226.

Laurie Scheiner/LAS
November 14, 2003

LAURIE SCHEINER
PRIMARY EXAMINER